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Name of Patentee: Nippon Hoechst Marion Roussel Ltd.

Title: Sustained Release Preparation of Oxybutynin Hydrochloride

What is Claimed is:

1. A sustained release preparation of oxybutynin hydrochloride which is characterized in that a gel-forming substance and a higher alcohol are compounded with a pharmaceutical composition containing oxybutynin hydrochloride and an acidic substance.

2. A sustained release preparation of oxybutynin hydrochloride according to claim 1 which is characterized in that 0.1-50 parts by weight of the acidic substance is contained to one part by weight of oxybutynin hydrochloride.

3. A sustained release preparation of oxybutynin hydrochloride according to claim 1 which is characterized in

that the gel-forming substance is hydroxypropyl methylcellulose (HPMC) or is a combination of HPMC with other gel-forming substance.

4. A sustained release preparation of oxybutynin hydrochloride according to claim 1 or 3 which is characterized in that an amount of HPMC or that of a combination of HPMC with other gel-forming substance in 100 parts by weight of the pharmaceutical composition containing oxybutynin hydrochloride is 10-70 parts by weight.

5. A sustained release preparation of oxybutynin hydrochloride according to claim 1 which is characterized in that an amount of the higher alcohol in 100 parts by weight of the pharmaceutical composition containing oxybutynin hydrochloride is 1-20 parts by weight.

Detailed Description of the Invention:

[Technical Field of the Invention]

The present invention relates to a sustained release pharmaceutical preparation of oxybutynin hydrochloride having a prolonged action which can be administered orally.

[Prior Art]

Sustained release drugs have advantages such as improvement in safety by prevention of rapid release of active ingredient, improvement in effectiveness by elongation of acting time, liberation from troublesome administration to the

patient by r ducing the administ ring times, and preventi n of noncompliance. Under the recent circumstance that urinary incontinence of aged people is becoming a social problem, effectiveness of oxybutynin hydrochloride which was developed as a remedy for frequent urination and urinary incontinence has been highly appreciated.

[Problems to be Solved by the Invention]

However, although oxybutynin hydrochloride is quickly absorbed after administration, its half life for disappearance is short and, therefore, said drug must be administered three times a day whereby it is troublesome for taking the drug. In addition, due to a symptom of patients suffering from urinary incontinence, their outing is often difficult and, for making their social life better, there has been a demand that the effect of oxybutynin hydrochloride which is a remedy for frequent urination and urinary incontinence is sustained and also prolonged by means of a prolonged action preparation having the above-mentioned advantages. In view of the above, the present inventors have conducted an intensive investigation and have found that, when oxybutynin hydrochloride is compounded with an acidic substance, a gel-forming substance and a higher alcohol, the drug can be released on a sustained basis whereupon the present invention has been achieved.

[Means for Solving the Problems]

A sustained releas preparation of oxybutynin

hydrochloride in accordance with the present inv ntion is characterized in that a gel-forming substance and a higher alcohol are compounded with a pharmaceutical composition containing oxybutynin hydrochloride and an acidic substance.

The present invention will be further illustrated as hereunder. Since oxybutynin hydrochloride is a salt of organic base with mineral acid, its solubility is predicted to become low under neutral to alkaline region. Sustained release preparations stay in a body for long time and it has been known that the pH values in human gastrointestinal tracts are, for example, 1-3.5 in stomach, 5-6 in duodenum, 6-7 in jejunum, and 8 in ileum. Thus, some contrivances in pharmaceutical preparations are necessary for keeping the solubility of a drug *in vivo* where pH varies as such. The present inventors have now solved the problems by adding an acidic substance for manufacturing a preparation which is not affected by pH whereby the sustained release preparation of the present invention has been obtained.

With regard to an acidic substance, any of inorganic and organic acids may be used although the use of organic acid which is nontoxic to human body is preferred. Examples of the organic acidic substance are adipic acid, ascorbic acid, erythorbic acid, citric acid, gluconic acid, glucono-δ-lactone, succinic acid, tartaric acid, fumaric acid, malic acid, aspartic acid, glutamic acid and alginic acid. Such an organic acid may be

used solely or two or more thereof may be used jointly. It is also possible to further combine with a salt of such an organic acid. Although an amount of the organic acid or salt thereof may vary depending upon the type of the acid and upon other substance to be compounded therewith, the amount as an organic acid is 0.1-50 parts by weight to one part by weight of oxybutynin hydrochloride. In the present invention, tartaric acid, succinic acid, citric acid or a salt thereof is used preferably and its amount to one part by weight of oxybutynin hydrochloride is 0.1-50 parts by weight or, preferably, 1-10 parts by weight in the case of tartaric acid for example. Such additives may be added to a mixture of oxybutynin hydrochloride and fillers for the drug in a powdery form or may be added after dissolving in water or alcohol.

When the pharmaceutical preparation is administered, a gel-forming substance is swollen in water to give a hydrophilic gel and rate of diffusion of the drug is controlled in the resulting gel layer. With regard to a gel-forming substance, any of commonly known and pharmaceutically acceptable ones may be used and examples of the applicable gel-forming substance are gum arabic, guar gum, agar, gelatin, sodium alginate, propylene glycol alginate, polyvinylpyrrolidone, polyvinyl alcohol, carboxyvinyl polymer, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethylcellulose and sodium carboxymethylcellulose. In

the present invention, one of them may be used sol ly or two or more of them may be used jointly. Preferably, hydroxypropyl methylcellulose (HPMC) or a combination of HPMC with other gel-forming substance is used.

With regard to a compounding amount of the gel-forming substance, it is necessary to add a specific amount so as to maintain the gelling of the preparation and, although the adding amount varies depending upon the substance used, it is 10-70 parts by weight or, preferably, 15-50 parts by weight in 100 parts by weight of a pharmaceutical preparation containing oxybutynin hydrochloride.

HPMC is put in the market in Japan under the trade name of Metolose by Shin-Etsu Chemical Co., Ltd. and, although various types are available, Metolose type 90SH or type 60SH having an average viscosity of 4,000 cps is particularly appropriate in the present invention. Amount of Metolose to be added to 100 parts of a pharmaceutical preparation containing oxybutynin hydrochloride is 10-70 parts by weight even when combined with other gel-forming substance or, preferably, 15-50 parts by weight.

Metolose is mixed in a powdery form with a pharmaceutical composition containing oxybutynin hydrochloride and the mixture may be directly compressed to make into a preparation of a desired shape or may be granulated by a common method and then made into a preparation by means of compression. Fillers

which are commonly used for pharmaceutical preparations such as lactose or crystalline cellulose are used for the pharmaceutical composition containing oxybutynin hydrochloride. If necessary, the granules or the tablets may be coated by a conventional method and colouring agent, plasticizer, antioxidant, stabilizer, etc. may be added thereto.

The sustained release agent prepared as such has a lag time until gel is sufficiently formed by contacting with water and, therefore, when an organic acid is added as in the present invention, the dissolution rate in initial stage by the organic acid becomes high whereby much amount of gel-forming substance is necessary for controlling the release. In order to solve such a problem, the present inventors have conducted an intensive investigation and found that a rapid release in initial stage can be suppressed when more than certain amount of higher alcohol having 12 or more carbons such as lauryl alcohol, cetanol, stearyl alcohol, oleyl alcohol or lanolin alcohol is added to the pharmaceutical preparation. Such a higher alcohol may be used either solely or jointly by combining two or more and, usually, it is used within a range of 0.5-10 parts by weight to 100 parts by weight of the pharmaceutical composition of oxybutynin hydrochloride.

Among the higher alcohol used in the present invention, the use of cetanol or stearyl alcohol is preferr d. Its amount

to 100 parts of the pharmaceutical preparation of oxybutynin hydrochloride is 0.5-10 parts by weight or, preferably, 1-5 parts by weight. Such a higher alcohol is dissolved in ethyl alcohol for example, added to a sustained release composition of oxybutynin hydrochloride and homogeneously mixed. The sustained release mixture prepared as such may be used after making into a desired preparation form such as capsules or tablets. In addition, the preparation may be coated with a high-molecular coating agent by a conventional method so that release of the drug can be delicately controlled.

[Function and Merit]

The sustained release oxybutynin hydrochloride tablets of the present invention prepared as such are able to control the release of oxybutynin hydrochloride and, as compared with the conventional preparations, they are capable of reducing the maximum concentration in plasma and of giving a constant concentration in blood for long time and, accordingly, it is now possible to afford a preparation of such a type that can be administered once or twice daily.

[Examples]

The present invention will be illustrated by way of the following examples.

Example 1.

Lactose (220 g), 40 g of crystalline cellulose (trade name: Avicel PH101; Asahi Chemical Industry) and 60 g of Metolos

60SH4000 (Shin-Etsu Chemical) were mixed. Then a solution of 6 g of oxybutynin hydrochloride, 10 g of stearyl alcohol (Kalcohl 86; Kao Corporation) and 20 g of citric acid dissolved in about 100 ml of ethyl alcohol was prepared and added to the above mixed powder little by little. After drying by a conventional method, 4 g of magnesium stearate were added to the resulting granules to lubricate followed by compressing to give tablets each weighing 180 mg.

Example 2.

Lactose (220 g), 40 g of crystalline cellulose and 60 g of Metolose 60SH4000 were mixed. Then a solution of 6 g of oxybutynin hydrochloride, 10 g of stearyl alcohol and 20 g of tartaric acid dissolved in about 100 ml of ethyl alcohol was prepared and added to the above mixed powder little by little. After drying by a conventional method, 4 g of magnesium stearate were added to the resulting granules to lubricate followed by compressing to give tablets each weighing 180 mg.

Example 3.

Lactose (236 g), 40 g of crystalline cellulose and 60 g of Metolose 60SH4000 were mixed. Then a solution of 6 g of oxybutynin hydrochloride, 10 g of succinic acid and 10 g of stearyl alcohol dissolved in about 100 ml of ethyl alcohol was prepared and added to the above mixed powder little by little. After drying by a conventional method, 4 g of magnesium stearate were added to th resulting granul s to lubricat followed by

compressing to give tablets each weighing 180 mg.

Example 4.

Lactose (80 g), 80 g of crystalline cellulose, 80 g of Metolose 60SH4000 and 80 g of sodium alginate (trade name: Kimitsu Algin I-5; Kimitsu Kagaku Kogyo) were mixed. Then a solution of 6 g of oxybutynin hydrochloride, 20 g of tartaric acid and 10 g of stearyl alcohol dissolved in about 100 ml of ethyl alcohol was prepared and added to the above mixed powder little by little. After drying by a conventional method, 4 g of magnesium stearate were added to the resulting granules to lubricate followed by compressing to give tablets each weighing 180 mg.

Comparative Example.

Oxybutynin hydrochloride (6 g) was mixed with 314.4 g of lactose and 36 g of crystalline cellulose, lubricated with 3.6 g of magnesium stearate and compressed so as to make one tablet 180 mg whereupon ordinary tablets were prepared.

Test Examples.

Releasing property (dissolution rate) and concentration in blood after administration were measured for the sustained release tablets and the ordinary tablets prepared in the above Examples and Comparative Example.

1) Measurement of dissolution rate of oxybutynin hydrochloride from each of the tablets was carried out according to the Dissolution Test Method of the Japanese Pharmacopoeia.

The dissolved solution was placed in a flask with 900 ml of the solution No. 1 (pH 1.2) or a phosphate buffer (pH 6.8), kept at 37℃ by warming and stirred at 100 rpm using a paddle. The test solution was sampled at 2, 4, 6, 8 and 10 hours thereafter and a solution in the same volume as that of the sampled solution was supplemented immediately to keep the volume of the solution constant. Incidentally, the sampled solution was subjected to a high performance liquid chromatography to determine the amount of oxybutynin hydrochloride.

2) For measurement of the changes in concentration in plasma upon administration to human being, blood was collected after 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hours from administration to human being and centrifuged to measure the concentration of the drug in plasma.

3) Result of the Test.

Figs. 1-4 show the result of the dissolution test for the preparations obtained in Examples and Formulation Example. Fig. 1 shows the result of the dissolution test at pH 1.2 and pH 6.8 of the ordinary tablets obtained in Comparative Example and of the tablets obtained in Example 1. Oxybutynin hydrochloride in the ordinary tablets was easily dissolved and the dissolution rate became 100% within several minutes while the tablets of Example 1 showed a sustained release property and, in addition, they were hardly affected by pH. Fig. 2, Fig. 3 and Fig. 4 are the results for the tablets of Example 2, Example 3 and Example

4, respectively and, lik in the cas of the preparation of Example 1, all of them show the sustained release property and the stability against pH. Then the ordinary tablets (2 tablets, each containing 3 mg) obtained in Comparative Example or the sustained release tablets (2 tablets, each containing 3 mg) were administered to four volunteers and the changes in oxybutynin hydrochloride concentration in plasma resulted thereby are shown in Fig. 5. As compared with the ordinary tablets, the sustained release tablets showed 4-fold of T_{max} and 1/4 of C_{max} whereby they were found to have a sustained release property.

Brief Explanation of Drawings:

Fig. 1 is a graph showing the result of the dissolution test at each pH of the ordinary tablets and of the tablets of Example 1.

Fig. 2 is a graph showing the result of the dissolution test of the tablets of Example 2.

Fig. 3 is a graph showing the result of the dissolution test of the tablets of Example 3.

Fig. 4 is a graph showing the result of the dissolution test of the tablets of Example 4.

Fig. 5 is a graph showing the changes of oxybutynin hydrochloride concentration in plasma when the ordinary tablets and the sustained release tablets of Example 1 were administered.

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の溶出試験の結果を示すグラフである。

【図２】図２は実施例２の錠剤の溶出試験の結果を示すグラフである。

【図３】図３は実施例３の錠剤の溶出試験の結果を示すグラフである。

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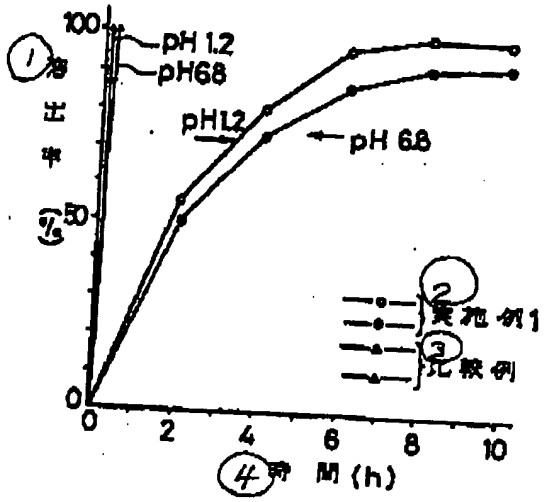
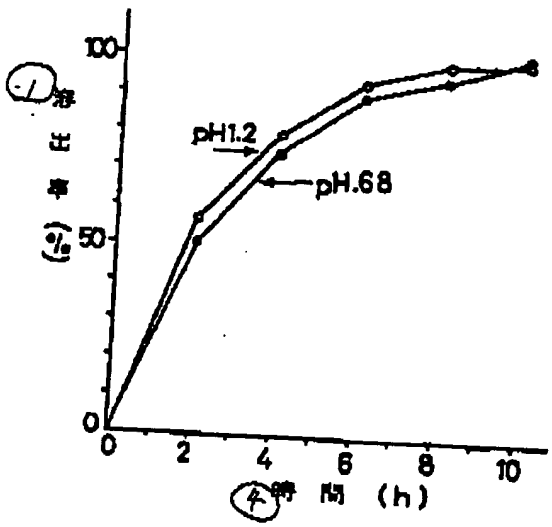
【図４】図４は実施例４の錠剤の溶出試験の結果を示すグラフである。

【図５】図５は普通錠と実施例１の徐放錠を投与したときの塩酸オキシプチニンの血漿中濃度推移を示すグラフである。

【図１】



【図２】



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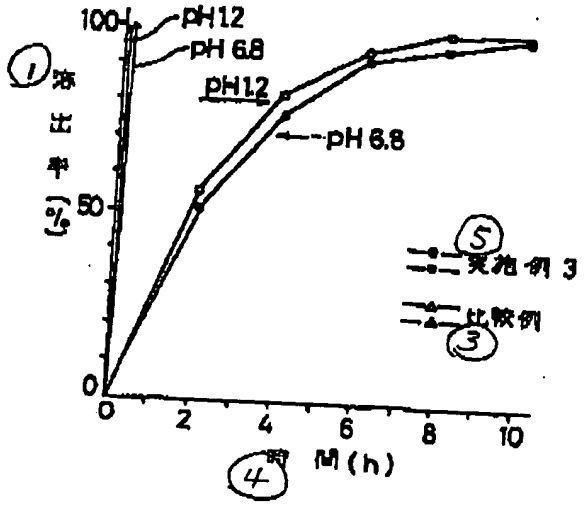

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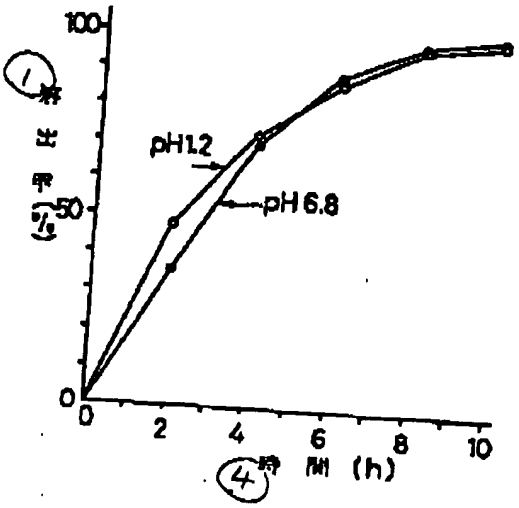

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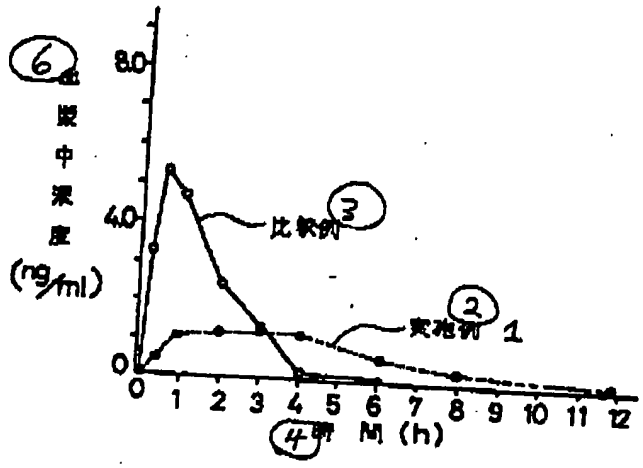

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(72)発明者 五十嵐 貴子
千葉県松戸市和名ケ谷957－5 小玉株式会社 生物科学研究所内

(72)発明者 八坂 勝義
茨城県猿島郡境町大字伏字宮西326－3 小玉株式会社 生物科学研究所内

In Figs. 1-5:

(1) Dissolution Rate

(2) Example 1

(3) Comparative Example

(4) Time

(5) Example 3

(6) Concentration in Plasma